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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/931,506	MITCHELL ET AL.
Examiner	**Art Unit**
Daniel M Sullivan	1636

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-218* is/are pending in the application.

4a) Of the above claim(s) *1-131, 168-181 and 205-218* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *132-147, 149-167, 182-186, 187, 192, 193, 195, 199-201, 203 and 204* is/are rejected.

7)☒ Claim(s) *148, 185, 188-191, 194, 196-198, 202* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *8*.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

This is the First Office Action on the merits of the application filed 16 August 2001 claiming benefit of the U.S. Provisional application 60/225,698 filed 16 August 2000. Claims 1-218 are pending in the application.

Applicant's election of Group III, claims 1, 132-167 and 182-204 in Paper No. 10 (filed 27 January 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 2-131, 168-181 and 205-218 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. In addition, the inclusion of claim 1, directed to a method for producing a decellularized tissue engineered construct, in Group III, drawn to a construct for use as a tissue engineering scaffold or for implanting into a subject, is an obvious typographical error as the method of claim 1 is distinct from the product of Group III for the reasons set forth on page 3 of the Election/Restriction requirement mailed 20 December 2002 (Paper No. 9). Therefore, claim 1 is also withdrawn from consideration.

Double Patenting

Applicant is advised that should claims 188, 192, 183 or 183-187 be found allowable, claims 191, 195 and 200-204, respectively, will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so

close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 143-145, 153 and 155 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 143-145 are indefinite in their recitation of "the biologically active agent". There is no antecedent basis for the limitation in claim 132, from which the claims depend. In the interest of compact prosecution, the claims have been examined on the merits with the assumption that Applicant intends that the claims depend from claim 142.

Claim 153 is indefinite in its recitation of "the length of tubing". There is no antecedent for the limitation in claim 133. In the interest of compact prosecution, the claims have been examined on the merits with the assumption that Applicant intends that the claims depend from claim 152.

Claim 155 is indefinite in its recitation of "the polymeric material". There is no antecedent for the limitation in claim 133. In the interest of compact prosecution, the claims have been examined on the merits with the assumption that Applicant intends that the claims depend from claim 154.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 132-138, 149-155, 157, 159, 161, 162 and 162 are rejected under 35 U.S.C. 102(b) as being anticipated by Bruchman *et al.* (1995) WO 95/29712 (hereinafter Bruchman '712) as evidenced by BD Biosciences description of Endothelial Cell Growth Supplement.

Bruchman '712 teaches a tissue engineered construct comprising a substrate seeded with cells and maintained under conditions suitable for growth of the cells for a growth period which is subsequently subjected to decellularization according to the methods of claims 132 and 133 (see especially page 6, paragraph 5; page 8, third full paragraph; and page 14, second full paragraph). Bruchman '712 further teaches the decellularized tissue engineered construct wherein: the growth period comprises a period sufficient for formation of a construct having a thickness of about less than 1 μm according to claim 134(see especially the second full paragraph on page 14); at least 80% of the cells are removed by decellularization according to claims 135-138(see especially page 14, line 26); the cells have been treated with a growth factor and serum during a first growth period according to claims 149 and 150 (see especially the formulation of ECGM in the second full paragraph on page 13 and the description of Endothelial Cell Growth Supplement from BD Biosciences (formerly Collaborative Biomedical Products)); the substrate comprises a synthetic polymer length of tubing coated with vascular smooth muscle cells according to claims 151-155, 157 and 159 (see especially page 10 and the second full

paragraph on page 11); and comprises at least two different cell types according to the limitations of claims 161 and 162 (see especially paragraph 1 and 2 on page 16).

The decellularized tissue engineered construct taught by Bruchman '712 is the same as the tissue engineered construct taught in the instant application; therefore the limitations of the claims are met by Bruchman '712.

Claims 132-138, 142-145, 149-155, 157, 159, 161, 162, 182, 186, 187, 192, 195, 203 and 204 are rejected under 35 U.S.C. 102(b) as being anticipated by Bruchman *et al.* (1997) WO 97/46266 (hereinafter Bruchman '266) as evidenced by BD Biosciences description of Endothelial Cell Growth Supplement.

Bruchman '266 teaches a tissue engineered construct comprising a substrate seeded with cells and maintained under conditions suitable for growth of the cells for a growth period which is subsequently subjected to decellularization according to the methods of claims 132 and 133 (see especially the paragraph bridging pages 7 and 8). Bruchman '266 further teaches the decellularized tissue engineered construct wherein: the growth period comprises a period sufficient for formation of a construct having a thickness of about less than 1 μm according to claim 134 (see especially the second full paragraph on page 18); at least 80% of the cells are removed by decellularization according to claims 135-138 (see especially page 19, first full paragraph); the cells have been treated with a growth factor and serum during a first growth period according to claims 149 and 150 (see especially the formulation of ECGM in the second full paragraph on page 17 and the description of Endothelial Cell Growth Supplement from BD Biosciences (formerly Collaborative Biomedical Products)); the substrate comprises a synthetic

polymer length of tubing coated with vascular smooth muscle cells according to claims 151-155, 157 and 159 (see especially the second full paragraph on page 14 and the first full paragraph on page 15); and comprises at least two different cell types according to the limitations of claims 161 and 162 (see especially the third full paragraph on page 23 and the second full paragraph on page 24).

Bruchman '266 also teaches the tissue engineered construct further comprises a biologically active agent (page 8, lines 9-10) selected from an agent to enhance recellularization (i.e., RGD; see especially Example 8), a pharmaceutical composition (see especially Example 6) and other agents (see especially page 12, third full paragraph) according to the limitations of claims 142-145.

Bruchman '266 further teaches embodiments wherein the biologically active agent is a cell according to the limitations of claim 182 (see especially page 12, third full paragraph) wherein: the decellularized tissue engineered construct has been treated with a growth factor and serum during a first growth period according to claims 186, 187, 203 and 204 (see especially the formulation of ECGM in the second full paragraph on page 17 and the description of Endothelial Cell Growth Supplement from BD Biosciences (formerly Collaborative Biomedical Products)); the decellularized tissue engineered construct is produced using cells according to claim 192 and 195 (see especially the second full paragraph on page 24).

The tissue engineered construct taught by Bruchman '266 is the same as the tissue engineered construct taught in the instant application; therefore the limitations of the claims are met by Bruchman '266.

Claims 132-138, 149-155, 157-159, 161, 162, 182, 186, 187, 192, 193, 195, 199, 203 and 204 are rejected under 35 U.S.C. 102(b) as being anticipated by Bruchman *et al.* (March 1999) U.S. Patent No. 5,879,383 (hereinafter Bruchman '383) as evidenced by BD Biosciences description of Endothelial Cell Growth Supplement.

Bruchman '383 teaches a tissue engineered construct comprising a substrate seeded with cells and maintained under conditions suitable for growth of the cells for a growth period which is subsequently subjected to decellularization according to the methods of claims 132 and 133 (see especially columns 5, 7 and 13). Bruchman '383 further teaches the decellularized tissue engineered construct wherein: the growth period comprises a period sufficient for formation of a construct having a thickness of about less than 1 μm according to claim 134 (see especially column 16, lines 56-60); at least 80% of the cells are removed by decellularization according to claims 135-138 (see especially column 17); the cells have been treated with a growth factor and serum during a first growth period according to claims 149 and 150 (see especially the formulation of ECGM, column 16, and the description of Endothelial Cell Growth Supplement from BD Biosciences (formerly Collaborative Biomedical Products)); the substrate comprises a synthetic polymer length of tubing or a flat surface coated with vascular smooth muscle cells according to claims 151-155 and 157-159 (see especially columns 14 and 15); and comprises at least two different cell types according to the limitations of claims 161 and 162 (see especially column 18).

Bruchman '383 further teaches embodiments wherein the decellularized construct is seeded with a cell according to the limitations of claim 182 (see especially columns 5 and 17-18) wherein: the decellularized tissue engineered construct has been treated with a growth factor and

serum during a first growth period according to claims 186, 187, 203 and 204 (see especially the formulation of ECGM in column 16 and the description of Endothelial Cell Growth Supplement from BD Biosciences (formerly Collaborative Biomedical Products)); the decellularized tissue engineered construct is produced using cells according to claim 192 (see especially column 18); the population of cells is autologous vascular endothelial cells according to claims 193 and 195 column 5, lines 30-32); and the construct is maintained for growth period under conditions suitable for growth of the population of cells according to claim 199 (see especially column 5, line 45).

The tissue engineered construct taught by Bruchman '383 is the same as the tissue engineered construct taught in the instant application; therefore the limitations of the claims are met by Bruchman '383.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 132 and 139-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Bruchman '712 (*supra*), Bruchman '266 (*supra*) or Bruchman '383 (*supra*).

The teachings of Bruchman '712, Bruchman '266 and Bruchman '383 with regard to claim 132 are described herein above. The art of record thus teaches all of the limitations of the dependent claims 139-141 except for a decellularized tissue engineered construct wherein least 90%, 95% or 99% are removed (claims 139-141 respectively). The limitations of claims 139-141 would, however, have been obvious to the ordinary skilled artisan based on the teachings of each of the citations alone because each of Bruchman '712, Bruchman '266 and Bruchman '383 teaches that scanning electron microscopy of representative samples confirmed nearly total loss of the native endothelium (see especially Bruchman '712 third full paragraph on page 14; Bruchman '266, page 19; and Bruchman '383, column 17).

Claims 132, 146 and 147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruchman '712 (*supra*) in view of Niklason *et al.* (1999) *Science* 284:489-493.

The teachings of Bruchman '712 with regard to claim 132 are described herein above. Bruchman '712 teaches all of the limitations of the claims except for a tissue engineered construct that has been subjected to a mechanical force or pulsatile stimulus during a first growth period. Bruchman '712 teaches that the tissue engineered constructs produced are to be used as vascular prostheses. Niklason *et al.* teaches a method of producing tissue engineered constructs similar to the tissue engineered constructs taught by Bruchman '712 (see especially the caption of Figure 1) and that culturing the constructs under pulsatile conditions produced superior results. In the third column on page 490, Niklason *et al.* teaches that vessels cultured under pulsatile conditions had a histologic appearance more similar to that of native arteries. In the middle column on page 491, Niklason *et al.* teaches that vessels grown without pulsatile stress possessed significantly less collagen and reduced suture retention strengths. In the middle column of page 492, Niklason *et al.* teaches that smooth muscle cells cultured under pulsatile conditions appear to be more highly differentiated and thus less prone to hyperplasia. Finally, in the paragraph bridging pages 492 and 493 and the first full paragraph on page 493, of Niklason *et al.* teaches that pulsed grafts remained open for 4 weeks *in vivo* while nonpulsed grafts developed thrombosis after 3 weeks.

It would have been obvious to one of ordinary skill in the art at the time the instant application was filed to modify the teachings of Bruchman '712 to include the pulsatile culture conditions of Niklason *et al.* in order to produce a superior graft. The teachings from Niklason *et al.* provide the motivation to combine the teachings because the constructs taught by Bruchman '712 are intended to be used as vascular grafts and Niklason *et al.* teaches that pulsatile culture conditions produce superior grafts. Absent evidence to the contrary, one would have a reasonable

expectation of success in combining the teachings because production of the decellularized construct according to the method of Bruchman '712 is not dependent upon the method by which the tissue engineered construct is established.

Claims 132, 146, 147, 182-184, 200 and 201 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Bruchman '266 (*supra*) or Bruchman '383 (*supra*) in view of Niklason *et al.* (1999) *Science* 284:489-493.

The teachings of Bruchman '266 and Bruchman '383 with regard to claim 132 and 182 are described herein above. Bruchman '266 and Bruchman '383 teach all of the limitations of the claims except for a tissue engineered construct that has been subjected to a mechanical force or pulsatile stimulus during a first growth period. Bruchman '266 and Bruchman '383 teach that the tissue engineered constructs produced are to be used as vascular prostheses. As described above, Niklason *et al.* teaches a method of producing tissue engineered constructs similar to the tissue engineered constructs taught by Bruchman '266 and Bruchman '383 and that culturing the constructs under pulsatile conditions produced superior results. It would have been obvious to one of ordinary skill in the art at the time the instant application was filed to modify the teachings of Bruchman '266 or Bruchman '383 to include the pulsatile culture conditions of Niklason *et al.* in order to produce a superior graft. The teachings from Niklason *et al.*, set forth above, provide the motivation to combine the teachings because the constructs taught by Bruchman '266 and Bruchman '383 are intended to be used as vascular grafts and Niklason *et al.* teaches that pulsatile culture conditions produce superior grafts. Absent evidence to the contrary, one would have a reasonable expectation of success in combining the teachings because

production of the decellularized construct according to the method of Bruchman '266 or Bruchman '383 is not dependent upon the method by which the tissue engineered construct is established.

Allowable Subject Matter

Claims 148, 185, 188-191, 194 and 196-198 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
March 26, 2003

JAMES KETTER
PRIMARY EXAMINER